UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/539,273	04/19/2006	Blas Cerda	Nen-22902/16	8503

37742 7590 09/19/2008

GIFFORD, KRASS, SPRINKLE, ANDERSON
& CITKOWSKI, P.C.
P.O. BOX 7021
TROY, MI 48007-7021

EXAMINER	
BARNHART, LORA ELIZABETH	
ART UNIT	PAPER NUMBER
1651	

MAIL DATE	DELIVERY MODE
09/19/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/539,273	CERDA, BLAS	
	Examiner	Art Unit	
	Lora E. Barnhart	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-57* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/19/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-57 as originally filed are currently pending.

Election/Restrictions

Applicant's election with traverse of the species “neonate or newborn,” “biotinidase,” and “amino acids” in the reply filed on 6/18/08 is acknowledged. The traversal is on the ground(s) that the species election is improper under the PCT rules. As discussed below, the claims are currently free of the prior art; however, if the claims are amended such that they are not free of the art, the election requirement may be reinstated.

Examination on the merits will commence on claims 1-57.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-57 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for screening an individual for screening individuals for a few inborn errors of metabolism caused by an enzyme deficiency in which activity levels of said enzyme are affected in the blood and in which a diagnostic substrate for said enzyme is known, does not reasonably provide enablement for screening an individual for any given inborn error of metabolism caused by any given enzyme. The specification does not enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands*, 858 F.2d 731, 737, 8 USPQd 1400, 1404 (Fed. Cir. 1988) (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the level of one of ordinary skill; (e) the level of predictability in the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. While all of these factors are considered, a sufficient number are discussed below so as to create a *prima facie* case.

The claims are broadly drawn to measuring the concentration of an analyte and the amount of a product of enzyme activity on a substrate in a sample obtained from an individual and determining whether said individual is affected by disorder that is an inborn error of metabolism. The specification and art fail to provide enablement for these claims across their entire breadth.

While many inborn errors of metabolism are known to be caused by a deficiency or mutation of a particular enzyme (such as carnitine metabolism errors as discussed in Chace (U.S. Patent 6,258,605); Gaucher's disease (glucocerebrosidase deficiency); and Fabry disease (a-galactosidase deficiency), to name a few), but not every disorder has been linked with a particular enzyme, and the specification provides no means for identifying the enzyme whose deficiency causes a given disease.

Furthermore, the specification provides no guidance for choosing the “metabolic analyte,” “the substrate [for the enzyme],” or the “reagent that inhibits the ability of the … enzyme to act on a corresponding substrate" for any given enzyme and any given disorder. Identifying analytes, solvents, and substrates for a given enzyme would require undue experimentation, since the mechanism and properties of each and every enzyme that can cause an inborn error of metabolism when mutated are not fully known.

Applicants present a single working embodiment in which the levels of various amino acids and acylcarnitines in blood samples are assessed (pages 37-38). The context of this assay is the diagnosis of biotinidase deficiency (page 37), but the working example includes no details as to how the data in the tables is indicative of the presence of this disorder. Applicants provide no specific information about the compositions of the analytes, solvents, and exogenous substrates that would allow the person of ordinary skill in the art to modify the claimed method for use in diagnosing additional diseases without undue experimentation. The working example does not employ the reagent at all, so it does not appear to exemplify the claimed invention. While a narrow working embodiment cannot be a sole factor in determining enablement, its limited showing, in light of the unpredictable nature of the art and the lack of direction applicants present, provides additional weight to the lack of enablement in consideration of the *Wands* factors as a whole. Thus, one of ordinary skill in the art would not have a reasonable expectation of success in using the claimed invention.

It is noted that claims 14 and 41 limit the enzyme to biotinidase; claims 15 and 22 limit the substrate to biocytin; and claims 16 and 43 limit the metabolic analyte to "one or more amino acids," but none of these claims defines an embodiment in which all necessary variables (the enzyme, the substrate, the analyte, and the reagent.

Claims 1-57 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

M.P.E.P. § 2163 recites, "An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention… one must define a compound by 'whatever characteristics sufficiently distinguish it'. A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process."

Independent claims 1, 28, and 54-57 require obtaining a sample from an individual, said sample containing "a metabolically indicative enzyme" (hereafter "the enzyme") and "one or more metabolic analytes" (hereafter "the analyte"). This sample also contains (or has added to it) a substrate for the enzyme (hereafter "the substrate") and "a reagent that inhibits the ability of [the enzyme] to act on [the substrate]"

(hereafter "the reagent"). These components, however, are not defined in terms of their structure, but rather solely in terms of their function.

For some biomolecules, examples of identifying characteristics include a sequence, structure, binding affinity, binding specificity, molecular weight, and length. Although structural formulas provide a convenient method of demonstrating possession of specific molecules, other identifying characteristics or combinations of characteristics may demonstrate the requisite possession. The “written description” requirement may be satisfied by using such descriptive means as words, structures, figures, diagrams, formulas, etc., that **fully set forth** the claimed invention. See *Noelle v. Lederman*, 355 F.3d 1343, 1349, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) and *Lockwood v. American Airlines, Inc.*, 107 F.3d at 1572, 41 USPQ2d at 1966. A definition by function alone “does not suffice” to sufficiently describe a coding sequence “because it is only an indication of what the gene does, rather than what it is.” *Regents of the University of California v. Eli Lilly & Co.,* 119 F.3 at 1568, 43 USPQ2d at 1406 (Fed. Cir. 1997). See also *Fiers v. Ravel*, 984 F.2d at 1169-71, 25 USPQ2d at 1605-06 (Fed. Clarification is required. 1993) (discussing *Amgen Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991)).

An adequate written description of a chemical invention also requires a precise definition, such as by structure, formula, chemical name, or physical properties, and not merely a wish or plan for obtaining the chemical invention claimed. See, e.g., *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 927, 69 USPQ2d 1886, 1894-95 (Fed. Cir. 2004). In *University of Rochester*, the patent at issue claimed a method of

selectively inhibiting PGHS-2 activity by administering a non-steroidal compound that selectively inhibits activity of the PGHS-2 gene product. However, the patent did not disclose any compounds that could be used in the claimed methods. While there was a description of assays for screening compounds to identify those that inhibit the expression or activity of the PGHS-2 gene product, there was no disclosure of which peptides, polynucleotides, and small organic molecules selectively inhibit PGHS-2. The court held that "[w]ithout such disclosure, the claimed methods cannot be said to have been described."). See M.P.E.P. § 2163.

In this case, the enzyme, the analyte, the substrate, and the reagent are described in the claims solely according to their function; that is, the enzyme is limited only in that it is "metabolically indicative" (i.e., that a change in its activity or concentration within an individual is altered as a result of a metabolic disorder in that individual; see page 8, lines 17-24, of the specification). Similarly, the analyte is described only by its function of being present in the sample. It should be noted that the analytes are not necessarily linked functionally in the claims to the enzyme; furthermore, at page 8, lines 26-31, of the as-filed specification, the term "metabolic analyte" is broadly defined as including any substance that is altered in amount, activity, or physical characteristic in the body of an individual with a metabolic disorder. The substrate is limited only in that it may "correspond" in some way to the enzyme and that the enzyme can act on it under some conditions to yield some product. Under the standard set in *Eli Lilly*, these chemical and biological elements of the claims are not adequately described in the specification to support the breadth of the claims.

Page 6, line 18, through page 8, line 15, of the as-filed specification lists several metabolic conditions that could be assayed using the instant method, but these conditions are not connected with any particular enzyme, analyte, substrate, or reagent that would be employed in the method to diagnose them. Page 12, lines 2-9, appear to indicate that the scope of the method is limited to diagnosing those conditions for which all of these variables are known, but the specification does not disclose even one such condition. It appears that the instant method is limited to diagnosing disorders that affect not only the activity or level of a known enzyme with a known substrate, but also the level, activity, or some other "physical characteristic" of some other molecule that would be present in the same sample as the enzyme. Table 1 at pages 17-19 is noted, but this table fails to indicate a reagent for these species, and some of the diseases in Table 1 do not appear to be correlated with either an enzyme or an analyte.

The specification contains no working examples in which the instant method was carried out to diagnose a particular disease using the instantly claimed method, so it does not appear to indicate that applicants possessed the entire invention, specifically the correlating aspect of the methods. At pages 36-37, the specification indicates that the levels of acylcarnitines and amino acids were assayed in blood samples to which had been added biocytin, a substrate for biotinidase (page 37, lines 7-16). However, the example does not indicate how this data "correlates" with the presence or absence of biotinidase deficiency in the individuals from which the blood samples were obtained.

The specification defines the enzymes, analytes, and substrates required to practice the claimed invention broadly and solely in terms of their function, and the

specification provides no guidance for identifying appropriate enzymes, analytes, and substrates for a given disease. Such "reach-through" claims were addressed by the Federal Circuit in *University of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 920-23, 69 USPQ2d 1886 (Fed. Cir. 2004). See M.P.E.P. § 2163.

Regarding the written description requirement in reach-through situations, the CAFC wrote, "While it is true that this court and its predecessor have repeatedly held that claimed subject matter 'need not be described *in haec verba*' in the specification to satisfy the written description requirement…it is also true that the requirement must still be met in some way so as to 'describe the claimed invention so that one skilled in the art can recognize what is claimed.' *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 323 F.3d 956, 963 at 968 (63 USPQ2d 1609) (Fed. Cir. 2002). We have further explained that:

> [T]he appearance of mere indistinct words in a specification or a claim, even an original claim, does not necessarily satisfy that requirement. … A description of an anti-inflammatory steroid, i.e., a steroid (a generic structural term) described even in terms of its function of lessening inflammation of tissues fails to distinguish any steroid from others having the same activity or function. A description of what a material does, rather than of what it is, usually does not suffice. [*Regents of the Univ. of Cal. v.] Eli Lilly [& Co., Inc.*], 119 F.3d [1559,] 1568 [43 USPQ2d 1398] [(Fed. Cir. 1997) ("Lilly")] … . The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described. *Id*.

Enzo, 323 F.3d at 968. Similarly, for example, in the nineteenth century, use of the word "automobile" would not have sufficed to describe a newly invented automobile; an inventor would need to describe what an automobile is, *viz.*, a chassis, an engine, seats, wheels on axles, etc. Thus, generalized language may not suffice if it does not convey the detailed identity of an invention." *Rochester*, 358 F.3d at 1892.

In sum, the instant specification does not provide any guidance that would steer the skilled practitioner toward enzymes, analytes, substrates, and reagents that can be used to carry out the claimed methods, an essential element of every claim of the application, and has not provided evidence that any such enzymes, analytes, substrates, and reagents were otherwise within the knowledge of a person of ordinary skill in the art at the relevant time. The disclosure is broad and vague and does not define any particular enzymes, analytes, and substrate that could be used in the instant method; the skilled artisan would not have immediately envisaged the materials necessary to practice the claimed method at the time of the invention.

Furthermore, new inborn errors of metabolism are being discovered continually. Years after the current invention, Sass et al. (2006, *American Journal of Human Genetics* 78: 401-409; reference U) discovered and characterized a novel inborn error of metabolism, aminoacylase 1 (ACY1) deficiency (Abstract). Sass et al. teach that while ACY2 deficiency causes a known disorder (Canavan disease), ACY1 deficiency had not, prior to their work, been reported to cause a metabolic disorder (page 401, column 2, paragraph 2). In 2003, therefore, the skilled artisan would not have reasonably concluded that applicant possessed the claimed invention across its entire scope, because the specification provides insufficient guidance for identifying the enzyme, analytes, and substrate for the disease characterized by ACY1 deficiency since this deficiency was unknown in the art at the time of filing. Skilled artisans did not know in 2003 about the ACY1 deficiency of Sass et al., so applicants could not possibly have possessed the appropriate analytes and substrates to screen for such a condition.

In short, the specification does not provide sufficient disclosure for the instant claims because it does not address newly discovered inborn errors of metabolism and how the instant method could be practiced.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-57 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Independent claims 1, 28, and 54-57 are drawn to methods of detecting a genetic disorder in an individual by determining the presence or amount of various analytes and enzymatic products, "wherein a determined presence or amount of said [analyte] and [product] correlates with presence or absence of said metabolic disorder." These claims do not particularly point out the manner in which the data obtained from the determination steps would be employed to generate a diagnosis. In *Metabolite Laboratories Inc. v. Laboratory Corp. of America Holdings*, 71 USPQ2d 1081 (Fed. Cir. 2004), the CAFC concluded that claims to methods of assaying or diagnosing require a "correlating" step in which a particular test result is correlated **unambiguously** with a particular conclusion. See *Metabolite Labs* at 1088, *e.g.* The claims fail to correlate the results (e.g., the presence of a given analyte or a particular level of the product) with a conclusion (e.g., a determination that the individual being tested has a given metabolic disorder). Claims 18-21 and 45-47 introduce the notion of comparison to internal

standards, but they fail to point out any particular comparisons or conclusions based on said comparisons. Clarification is required.

Because claims 2-27 and 29-53 depend variously from indefinite claims 1 and 28 and do not clarify the point of confusion, they must also be rejected under 35 U.S.C. 112, second paragraph.

Furthermore, step (1) of claim 1 requires contacting a sample with “one or more substrates” for the enzymes resident within the sample under conditions in which said enzymes can act on “a corresponding substrate” to yield a product. The relationship between the “one or more substrates” and the “corresponding substrate” is not clear. Claims 28 and 54-57 suffer similar deficiencies. Clarification is required.

Claims 18-21 and 45-47 require adding “reference substrates" or "reference products" to the sample, but it is not clear to what these substances and products are referring. Clarification is required.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to

be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-57 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-11, 16-27, and 40 of copending Application No. 10/539,180. Although the conflicting claims are not identical, they are not patentably distinct from each other because the scope of the instant claims completely encompasses the scope of the cited claims in the ‘180 application.

The independent claims in the instant application (1, 28, and 54-57) and in the ‘180 application (1 and 40) are drawn to methods for detecting metabolic disorders by contacting a sample containing an enzyme and analytes with a composition comprising a substrate for the enzyme such that the enzyme works on the substrate to produce a product, stopping the enzymatic reaction with an agent, and determining the amount of analytes and product in the sample; in the ‘180 application, the disorder is limited to a biotinidase deficiency and one or more other deficiencies, the enzyme is biotinidase, the analyte is amino acids or carnitines, and the product is biotin (instant claims 14, 15, 41, and 42 so limit the independent claims). Instant claims 2-4 and 29-31 correspond to claims 2-4 in the '180 application. Instant claims 5, 10, 11, 32, 37, and 38 correspond to claims 5, 10, and 11 of the '180 application. Instant claims 6-9 and 33-36 correspond to claims 6-9 of the ‘180 application. Instant claims 16, 17, 43, and 44 correspond to claims 16 and 17 of the ‘180 application. Instant claims 18-26 and 45-51 correspond to

claims 18-26 of the '180 application. Instant claims 27 and 52 correspond to claim 27 o the '180 application. Instant claims 53-57 address multiple samples, as does claim 40 of the '180 application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

No claims are allowed.

Applicant is requested to specifically point out the support for any amendments made to the disclosure in response to this Office action, including the claims (MPEP 714.02 and 2163.06). In doing so, applicant is requested to refer to pages and line numbers in the as-filed specification, **not** the published application. Due to the procedure outlined in MPEP § 2163.06 for interpreting claims, it is noted that other art may be applicable under 35 U.S.C. § 102 or 35 U.S.C. § 103(a) once the aforementioned issue(s) is/are addressed.

Applicant is requested to provide a list of all copending U.S. applications that set forth similar subject matter to the present claims. A copy of such copending claims is requested in response to this Office action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lora E. Barnhart whose telephone number is 571-272-1928. The examiner can normally be reached on Monday-Thursday, 9:00am - 5:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn can be reached on 571-272-0926. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lora E Barnhart/
Primary Examiner, Art Unit 1651